

André Nadeau

Functional Hypoglycemia: Facts and Fancies

SUMMARY

When blood glucose decreases below a given threshold, symptoms of cerebral dysfunction and/or adrenergic hyperactivity appear. If this occurs postprandially in otherwise normal subjects, a diagnosis of reactive or functional hypoglycemia may be proposed. However, these symptoms are not specific, and they should coincide with low blood glucose values and be rapidly relieved by glucose ingestion before a diagnosis of hypoglycemia is confirmed. The oral glucose tolerance test, often used in the evaluation of such patients, also may give misleading results, because many normal subjects have glucose values below the 'normal' range during the test. This may explain why functional hypoglycemia has probably been overdiagnosed during the last several years, giving rise to a description of the syndrome of non-hypoglycemia, in which the patient's symptoms are falsely attributed to hypoglycemia, either by himself or by his physician. Nevertheless, functional hypoglycemia exists and can be improved by proper management. (Can Fam Physician 1984; 30:1333-1335)

SOMMAIRE

Lorsque la glycémie s'abaisse en bas d'un certain seuil, il y a apparition de symptômes de dysfonctionnement cérébral et/ou d'hyperactivité adrénergique. Lorsque ceci survient après le repas chez une personne par ailleurs normale, un diagnostic d'hypoglycémie réactionnelle ou fonctionnelle peut être avancé. Néanmoins, ces symptômes ne sont pas tellement spécifiques, et ils devraient coïncider avec des valeurs glycémiques basses et se corriger rapidement suite à l'ingestion de glucose avant de porter le diagnostic d'hypoglycémie. L'épreuve d'hyperglycémie provoquée par voie orale souvent utilisée dans l'évaluation de ces patients peut également donner des résultats trompeurs, car beaucoup de sujets normaux présentent des glycémies en bas de la "normale" lors de ce test. Ceci explique sans doute pourquoi le diagnostic d'hypoglycémie fonctionnelle a été surutilisé depuis plusieurs années, amenant la description du syndrome de non-hypoglycémie qui consiste à attribuer par erreur les symptômes à de l'hypoglycémie, soit par le patient lui-même ou même par son médecin. Néanmoins, l'hypoglycémie fonctionnelle existe et peut être améliorée par un traitement approprié.

Dr. Nadeau is an associate professor of medicine at Laval University, and Director, Laboratoires de Recherche en Endocrinologie et Métabolisme, Le Centre Hospitalier de l'Université Laval, Ste-Foy. Reprint requests to: Le Centre Hospitalier de l'Université Laval, 2705, Laurier Blvd., Ste-Foy, PQ. G1V 4G2.

SHORTLY AFTER the discovery of insulin in 1924, Harris¹ reported five nondiabetic subjects with symptoms similar to those occurring during an insulin reaction in insulin-treated diabetic patients. He was probably the first to postulate that hyperinsulinism or dysinsulinism could well represent

the pathological counterpart to diabetes mellitus. Many years later, the concept of hypoglycemia evolved into a broad classification encompassing many different and unrelated pathological entities.² This is not really surprising, because blood glucose is normally controlled by many biochemical factors (enzymes) and physiological factors (hormones) located in many different organs. Various inherited or acquired pathological processes can alter these factors.

By definition, hypoglycemia is a biochemical abnormality (i.e., a blood glucose value below the normal range). Unfortunately, defining the normal range of blood or plasma glucose is not as simple as it may seem. While for practical purposes, plasma

glucose in the range of 70-100 mg/dl is considered normal,³ more than five percent of normal subjects are expected to have values outside these limits. Furthermore, to be considered part of a disease entity, low blood glucose concentration should be associated with disturbance in some body functions. This is particularly important if glucose is measured after a glucose challenge, such as that done during an oral glucose tolerance test. Studies conducted in large population samples^{2, 4} have shown that many normal subjects may have plasma glucose values below 50 mg/dl without any symptoms. On the other hand, other people may experience typical symptoms with values in the 50-70 mg/dl range and even above 70 mg/dl. Thus,

diagnosis of reactive or post-prandial hypoglycemia depends on more or less subjective clinical manifestations.

Clinical Manifestations Of Hypoglycemia

The clinical manifestations of hypoglycemia can be grouped under two headings: those caused by neuroglucopenia, and those induced by adrenergic overactivity.

Glucose is the major fuel of the brain. The central nervous system continuously uses glucose and oxygen to function. If the supply of glucose diminishes, then symptoms of neuroglucopenia appear. Depending on the severity of the glucose shortage, subjects may experience fatigue, headache, visual disturbances, faintness, difficulty with speech and thinking, confusion and even seizures and coma. Psychiatric manifestations such as outbursts of temper or bizarre behavior may also occur.^{3, 5}

Activation of the autonomic nervous system and the ensuing release of epinephrine by the adrenal medulla cause the signs and symptoms of adrenergic overactivity. These symptoms include sweating, palpitations, tachycardia, shakiness, anxiety, nervousness or pallor.^{3, 5}

Some subjects feel hungry, but nausea and vomiting also may be present.

While the neuroglucopenic symptoms usually predominate with the gradual onset of fasting hypoglycemia, the adrenergic manifestations normally predominate with the more rapid onset of postprandial or reactive hypoglycemia. Nevertheless, both groups of symptoms, or either alone, may be observed in reactive hypoglycemia.⁵

With the functional type of reactive hypoglycemia, the symptoms typically develop 90 minutes to two hours after a meal, most often after breakfast. The symptoms are transitory and usually subside in 15-30 minutes. Convulsions and loss of consciousness are unusual, and their presence should always suggest that other causes of hypoglycemia, particularly insulinoma, be sought. Reactive hypoglycemia also may be present three to five hours after a meal, and appears to be associated with a special type of diabetes mellitus in which the insulin response to glucose is quantitatively important but delayed. This causes abnormally high blood glucose values during the two to three hours following glucose ingestion

and then a rapid drop in blood glucose concentration and a typical hypoglycemic attack.⁵

Although functional hypoglycemia is manifested more specifically by episodes of the symptoms mentioned above, sometimes patients mainly complain of more chronic disabilities such as progressive fatigue, lack of energy, depressed mood or emotional instability. Although it is well known that functional hypoglycemia is associated with emotional disturbance and personality disorder, it is not clear whether hypoglycemia is the cause or the consequence of such disturbances.⁶

Hypoglycemia Vs. 'Non-Hypoglycemia'

Obviously, neither the neuroglucopenic nor the adrenergic symptoms mentioned above are specific and everybody has probably experienced some of them. For many years, hypoglycemia has attracted the public press, which is always attentive to the public's desire for information about health matters.^{2, 5} Often, after reading a magazine article on the subject, a patient will visit me with his own diagnosis of hypoglycemia. In the U.S., the diagnosis of hypoglycemia seems to have reached epidemic proportions in recent years.⁷ Looking at this phenomenon, Yager and Young described the syndrome of non-hypoglycemia.⁷ These authors reported their own experience with many patients who accounted for their symptoms by falsely attributing them to hypoglycemia. Such a diagnosis has the obvious advantage of being more socially acceptable than a psychologic or otherwise stigmatizing condition. Furthermore, the mere fact of having a medical diagnosis for ambiguous and often perplexing symptoms can provide some relief to these subjects. Finally, the more or less 'ritual' approach of adhering to a strict diet and/or taking multiple daily tablets of vitamins as proposed in the public press appears to be an easy way to cope with symptoms, and fits well with the compulsive habits of most of these people.

Theoretically, the diagnosis of non-hypoglycemia should be easy to make; it requires only the demonstration that glucose metabolism is normal and that no relation exists between blood sugar level and the patient's symptoms.⁷ To do this, the usual approach is to per-

form a five-hour glucose tolerance test, with blood samples taken at 30-minute intervals after an overnight fast.^{5, 6} Unfortunately, as noted above, many asymptomatic normal subjects may have glucose values below the so-called normal range; because of this, probably many patients with non-hypoglycemia have been misdiagnosed by their physician as suffering from reactive hypoglycemia. In such cases, failure to recognize non-hypoglycemia may preclude further exploration of alternative diagnoses and treatments, and this should always be kept in mind when a diagnosis of hypoglycemia is proposed.

Diagnosis Of Reactive Hypoglycemia

Proper diagnosis of reactive hypoglycemia (or any other type of hypoglycemia) requires that there is a typical symptomatic attack, which is associated with a low plasma or blood glucose, and that relief of symptoms is rapid after glucose administration. However, this triad, known as the triad of Whipple, is rarely demonstrated spontaneously, and provocative tests are usually needed.⁵ Although the appropriateness of the oral glucose tolerance test has been challenged,⁸ it remains the more standardized approach to assess glucose homeostasis. To be diagnostic of reactive hypoglycemia, the appearance of symptoms during the test should coincide with the nadir of plasma glucose. Measurements of plasma cortisol and/or epinephrine have been used to demonstrate the activation of the hypothalamic pituitary-adrenal axis in response to the central neuroglucopenic stress. However, the significance of these measurements should be more clearly established before their general use is advocated. Finally, although subjects with reactive hypoglycemia may, as a group, differ in their plasma insulin curve from normal subjects, abnormalities in the individual pattern of insulin response are rarely found, with the exception of patients with diabetic reactive hypoglycemia. Insulin measurements should be limited to special investigation only.

Treatment Of Reactive Hypoglycemia

Once a diagnosis of reactive hypoglycemia has been made, the available

therapeutic modalities should be discussed with the patient.

Probably the most important aspect of managing such patients is to give them simple but clear and precise explanations about their problem. For those who have experienced the distressing symptoms of an acute adrenaline discharge, the relationship between their unpleasant feelings and a simple disturbance in blood glucose homeostasis may not be self-evident. However, such patients may easily understand and accept that after a meal, blood glucose normally goes up and then goes down; maintenance of blood glucose concentration within a normal narrow range is controlled by a very sophisticated body system that sometimes appears to be hypersensitive, thus causing reactive hypoglycemia, with possibly all the subsequent neuroglucopenic and hyperadrenergic symptoms previously described. Such patients may be reassured by knowing that this response more or less resembles the situation when the fear normally experienced at the sight of a small animal (e.g., a mouse) is exaggerated to the point of faintness, and does not correspond to any serious illness. Along with some improvement in the anxiety associated with this particular problem, such detailed explanations on the physiopathogenesis of the hypoglycemic attack often permit the patient to detect the initial symptoms of his episodes and alleviate them by immediately taking a small amount of sugar.

The patient should then be instructed that the more specific approach to prevent the hypoglycemic episodes is dietetic; it has long been recognized that these patients usually benefit from small and frequent meals and a low carbohydrate diet (refined sugars should be totally excluded), which is high in protein.^{9, 10} An increase in alimentary fibers is also advocated.

If such measures are not adequate to permit patients with reactive hypoglycemia to live normally, then drugs may be considered. However, drug therapy of reactive hypoglycemia is mainly empirical, as suggested by the diversity of recommended agents. These include sedatives, tranquilizers, sulfonylureas, anticholinergics, biguanides, diphenylhydantoin and propranolol.⁵ In my experience, a short-acting sulfonylurea such as tolbutamide is useful in patients with

reactive hypoglycemia of the diabetic type. In those with the functional type of reactive hypoglycemia, an anticholinergic drug taken 30 minutes before meals may be beneficial; possibly it diminishes the influence of foods on the insulinogenic gastrointestinal hormones. When prescribing such drugs, the physician should be aware of the fact that reactive hypoglycemia is a chronic disorder and that medication may be needed for many years.

Conclusion

Reactive hypoglycemia is a condition which is not easily diagnosed. The demonstration of typical symptoms associated with low blood glucose is imperative. Unfortunately, the commonly used oral glucose tolerance test is a very imperfect way of documenting reactive hypoglycemia,⁸ and caution should be taken to distinguish between hypoglycemia and non-hypoglycemia.

Once the diagnosis of functional hypoglycemia is established, diet therapy is usually effective, but explanations and reassurance of the patient are integral parts of management. Drug therapy should be limited to subjects who do not benefit greatly from dietary measures.

References

1. Harris S: Hyperinsulinism and dysinsulinism. *JAMA* 1924; 83:729-733.
2. Hofeldt FD: Reactive hypoglycemia. *Metabolism* 1975; 24:1193-1208.
3. Gastineau CF: Is reactive hypoglycemia a clinical entity? *Mayo Clin Proc* 1983; 58:545-549.
4. Lev-Ran A, Anderson RW: The diagnosis of postprandial hypoglycemia. *Diabetes* 1981; 30:996-999.
5. Permutt MA: Postprandial hypoglycemia. *Diabetes* 1976; 25:719-736.
6. Anthony D, Dippe S, Hofeldt FD, et al: Personality disorder and reactive hypoglycemia. A quantitative study. *Diabetes* 1973; 22:664-675.
7. Yager J, Young RT: Non-hypoglycemia is an epidemic condition. *N Engl J Med* 1974; 291:907-908.
8. Hogan MJ, Service FJ, Sharbrough FW et al: Oral glucose tolerance test compared with a mixed meal in the diagnosis of reactive hypoglycemia. A caveat on stimulation. *Mayo Clin Proc* 1983; 58:491-496.
9. Conn JW: The advantage of a high protein diet in the treatment of spontaneous hypoglycemia. *J Clin Invest* 1936; 15:673-678.
10. Thorn GW, Quinby JT, Clinton M Jr: A comparison of the metabolic effects of isocaloric meals of varying composition, with special reference to the prevention of postprandial hypoglycemic symptoms. *Ann Intern Med* 1943; 18:913-919.

Beconase®

(beclomethasone dipropionate)

Prescribing Information

Indications and clinical uses

Beconase is indicated for the treatment of perennial and seasonal allergic rhinitis unresponsive to conventional treatment

Contraindications

Active or quiescent tuberculosis or untreated fungal, bacterial and viral infections. Children under six years of age

Warnings

In patients previously on high doses of systemic steroids, transfer to Beconase may cause withdrawal symptoms such as tiredness, aches and pains, and depression. In severe cases, adrenal insufficiency may occur, necessitating the temporary resumption of systemic steroids. The safety of Beconase in pregnancy has not been established. If used, the expected benefits should be weighed against the potential hazard to the fetus, particularly during the first trimester of pregnancy.

Precautions

The replacement of a systemic steroid with Beconase has to be gradual and carefully supervised by the physician. The guidelines under Administration should be followed in all such cases. Unnecessary administration of drugs during pregnancy is undesirable. Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and hematological status should be periodically assessed. Fluorocarbon propellants may be hazardous if they are deliberately abused. Inhalation of high concentrations of aerosol sprays has brought about cardiovascular toxic effects, and even death, especially under conditions of hypoxia. However, evidence attests to the relative safety of aerosols when used intranasally and with adequate ventilation.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

During Beconase therapy, the possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

Adverse reactions

No major side-effects attributable to Beconase have been reported. Occasional sneezing attacks have followed immediately after the use of the intranasal aerosol. A few patients have complained of burning sensation and irritation in the nose after Beconase Nasal Inhalation. When patients are transferred to Beconase from a systemic steroid, allergic conditions such as asthma or eczema may be unmasked.

Dosage and administration

The usual dose for patients of all ages who received no previous systemic steroid is one application (50 mcg of beclomethasone dipropionate) to each nostril three to four times daily. Maximum daily dose should not exceed twenty applications in adults and ten applications in children. If Beclomethasone is used concurrently, the maximum dose of each aerosol is ten applications in adults and five applications in children. Beconase should not be used under six years of age.

Since the effect of Beconase depends on its regular use, patients must be instructed to take the nasal inhalations at regular intervals and not as with other nasal sprays, as they feel necessary. They should also be instructed in the correct method, which is to blow the nose, then insert the nozzle firmly into the nostril, compress the opposite nostril and actuate the aerosol while inspiring through the nose, with the mouth closed.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases it is advisable to use a nasal vasoconstrictor for two to three days prior to Beconase.

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to Beconase. Initially, Beconase and the systemic corticosteroid must be given concomitantly, while the dose of the latter is gradually decreased. The usual rate of withdrawal of the systemic steroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the previous dose of the systemic steroid should be resumed for a week before further decrease is attempted.

Dosage form

Beconase is a metered-dose aerosol, delivering 50 micrograms of beclomethasone dipropionate with each depression of the valve. There are two hundred doses in a container.

Official product monograph on request



AH Allen & Hanburys
A Glaxo Canada Ltd. Company
Toronto, Montreal